WEST Search History

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DATE: Wednesday, October 13, 2004

Hide?	Set Name	Query	Hit Count
		DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L11	(compliment adj1 activation) and (taxol or taxane or paclitaxel)	0
☐	L10	L9 and complement$	6
☐	L9	(cremophor) same hypersensitiv$	89
☐	L8	(compliment adj1 activation) and polyethoxy$	0
☐	L7	(compliment adj1 activation) and cremophor$	0
☐	L6	(compliment adj1 activation) and cremophor	0
☐	L5	(compliment adj1 activation) same hypersensitiv$	0
		DB=USPT; PLUR=YES; OP=OR	
☐	L4	6114358.pn.	1
☐	L3	5852051.pn.	1
☐	L2	4980495.pn.	1
		DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L1	cremophor same (complement)	1

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L1: Entry 1 of 1 File: USPT Jan 27, 2004

DOCUMENT-IDENTIFIER: US 6683055 B1
TITLE: Low molecular weight inhibitors of complement proteases

Brief Summary Text (5):
The activation of the complement is associated with the following disorders or pathophysiological conditions (Liszewski, M. K.; Atkinson, J. P.: Exp. Opin. Invest. Drugs 7(3) (1998): 324-332; Morgan, B. P.: Biochemical Society Transactions 24; (1996), 224-9; Morgan, B. P.: Critical Review in Clinical Laboratory Sciences 32 (3); (1995), 265-298; Hagmann, W. K.; Sindelar, R. D.: Annual reports in medicinal chemistry 27, (1992), 199 et seq.; Lucchesi, B. R.; Kilgore, K. S.: Immunopharmacology 38 (1997), 27-42; Makrides, S. C.: Pharmacological Reviews 50(1) (1998), 59-85) Reperfusion injuries after ischemias; ischemic conditions, during, for example, operations with the aid of heart-lung machines; operations in which blood vessels are clamped off generally for avoiding major hemorrhages; myocardial infarction; thromboembolic cerebral infarction; pulmonary thrombosis, etc.; Hyperacute organ rejection; especially in xenotransplantations; Organ failure, e.g. multiple organ failure or ARDS (adult respiratory distress syndrome); Disorders due to trauma (cranial trauma) or multiple injury, e.g. thermal injury (burns); Anaphylactic shock; Sepsis; "vascular leak syndrome": in the case of sepsis and after treatment with biological agents, such as interleukin-2 or after transplantation; Alzheimer's disease and other inflammatory neurological disorders, such as myastenia graevis, multiple sclerosis, cerebral lupus, Guillain-Barre syndrome; meningitis; encephalitis; Systemic lupus erythematosus (SLE); Rheumatoid arthritis and other inflammatory disorders of the rheumatoid disorder group, e.g. Behcet's Syndrome; Juvenile rheumatoid arthritis; Renal inflammations of various origin, e.g. Glomerulonephritis, Lupus nephriti; Pancreatitis; Asthma; chronic bronchitis; Complications during dialysis in the case of kidney failure; Vasculitis; thyroiditis; Ulcerative colitis and other inflammatory disorders of the gastrointestinal tract; Autoimmune diseases. It is possible that complement plays a role in spontaneous abortions, based on immunological rejection reactions (Giacomucci E., Bulletti C., Polli V., Prefetto R A., Flamigni C., Immunologically mediated abortion (IMA). Journal of Steroid Biochemistry & Molecular Biology, 49(2-3) (1994), 107-21). Here, it is possible that modulation of the immunological rejection reaction is achieved by inhibition of the complement system and hence the rate of abortions is correspondingly reduced. Complement activation plays a role in the case of side effects of drugs. Liposome-based therapies which are used, for example, in cancer treatment may be mentioned as an example here. Hypersensitive reactions have been observed in patients who have been treated with drug formulations based on liposomes (Transfusion 37 (1997) 150). Activation of the complement system has also been demonstrated for other excipients used in drug formulations, e.g. Cremophor EL (Szebeni, J. et al. Journal of the National Cancer Institute 90 (4); 1998). The complement activation may therefore be responsible for the anaphylactoid reactions observed in some cases. Inhibition of the complement system, for example by the C1s inhibitors mentioned here, should therefore alleviate the side effects of medicaments based on activation of the complement system and reduce resulting hypersensitivity reactions.

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L9: Entry 6 of 89 File: USPT May 4, 2004

DOCUMENT-IDENTIFIER: US 6730698 B2
TITLE: Method and compositions for administering taxanes orally to human patients

Detailed Description Text (36):
Further advantages of the present invention are in the area of safety. Because of its physico-chemical properties, paclitaxel must be solubilized in a Cremophor/ethanol mixture and that vehicle may be responsible for at least some of the allergic-type reactions experienced by patients on paclitaxel therapy. Other solubilizing agents have been used but none have been as suitable as Cremophor/ethanol. Paclitaxel must be given slowly to patients, with medical personnel in a state of constant vigilance for severe hypersensitivity reactions. For standard intravenous regimens, pre-medication regimens of H-1 and H-2 blockers plus steroids are generally required. However, even when Cremophor/ethanol solubilization is not used, intravenous taxanes can still bring about severe reactions following intravenous use. Thus, docetaxel administration is associated with anasarca and other reactions. Therapies with the potential to eliminate or diminish the need for pre-medication in these settings would be very valuable clinically.

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L9: Entry 9 of 89 File: USPT Feb 10, 2004

DOCUMENT-IDENTIFIER: US RE38424 E
TITLE: Method for treating taxol side-effects with G-CSF

Detailed Description Text (30):
Taxol and/or its cremophor-ethanol vehicle have been demonstrated to cause hypersensitivity reactions and can cause cardiac dysrhythmias. Therefore, all cycles of taxol were given by continuous intravenous infusion over 24 hours with premedication. This premedication consisted of dexamethasone (20 mg orally or intravenously at 14 and 7 hours prior to taxol) and cimetidine (300 mg with diphenhydramine 50 mg intravenously 30 minutes prior to initiation of the taxol infusion). Each patient's first cycle of taxol was given in the medical intensive care unit, this allowed for continuous cardiac monitoring of the patient. Subsequent cycles of taxol were given on the inpatient oncology unit for patients having asymptomatic bradycardia or no cardiovascular toxicity on the first cycle. Patients manifesting second or third degree heart block had remaining cycles given in the intensive care unit with appropriate interventions. Antiemetics were given as needed.

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L9: Entry 30 of 89 File: USPT May 28, 2002

DOCUMENT-IDENTIFIER: US 6395770 B1

**** See image for Certificate of Correction ****

TITLE: Method and compositions for administering taxanes orally to human patients

Detailed Description Text (36):

Further advantages of the present invention are in the area of safety. Because of its physico-chemical properties, paclitaxel must be solubilized in a Cremophor/ethanol mixture and that vehicle may be responsible for at least some of the allergic-type reactions experienced by patients on paclitaxel therapy. Other solubilizing agents have been used but none have been as suitable as Cremophor/ethanol. Paclitaxel must be given slowly to patients, with medical personnel in a state of constant vigilance for severe hypersensitivity reactions. For standard intravenous regimens, pre-medication regimens of H-1 and H-2 blockers plus steroids are generally required. However, even when Cremophor/ethanol solubilization is not used, intravenous taxanes can still bring about severe reactions following intravenous use. Thus, docetaxel administration is associated with anasarca and other reactions. Therapies with the potential to eliminate or diminish the need for pre-medication in these settings would be very valuable clinically.

CLAIMS:

19. A method of preventing or reducing hypersensitivity and allergic reactions in human patients undergoing taxane therapy for a taxane-responsive disease condition comprising orally co-administering to the patient a taxane with or without Cremophor, and a bioavailability enhancing agent, without prior administration of medication to prevent the hypersensitivity or allergic reactions, whereby taxane achieves therapeutically effective blood levels.

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L9: Entry 42 of 89 File: USPT Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096331 A
TITLE: Methods and compositions useful for administration of chemotherapeutic agents

Brief Summary Text (10):
Wiernik et al. in "Phase I Clinical and Pharmacokinetic Study of Taxol," Cancer Research, 47, 2486-2493 (May 1, 1987), also report the administration of taxol in a cremophor vehicle by IV infusion over a 6-hour period in a Phase I study. Grade 3-4 hypersensitivity reactions incurred in 4 of 13 courses. The starting dose for the study was 15 mg/m.sup.2 (one-third of the lowest toxic dose in dogs). Doses were escalated, and a minimum of 3 patients were treated at each dose level until toxicity was identified, and then 4-6 patients were treated at each subsequent level. The study concluded that neurotoxicity and leukopenia were dose-limiting, and the recommended Phase II trial dose was 250 mg/m.sup.2 with premedication.

Detailed Description Text (3):
Capxol.TM. is a novel, cremophor-free formulation of the anticancer drug paclitaxel. The inventors, based on animal studies, believe that a cremophor-free formulation will be significantly less toxic and will not require premedication of patients. Premedication is necessary to reduce the hypersensitivity and anaphylaxis that occurs as a result of cremophor in the currently approved and marketed BMS (Bristol Myers Squibb) formulation of paclitaxel. Capxol.TM. is a lyophilized powder for reconstitution and intravenous administration. When reconstituted with a suitable aqueous medium such as 0.9% sodium chloride injection or 5% dextrose injection, Capxol.TM. forms a stable colloidal solution of paclitaxel. The size of the collodial suspension may range from 20 nm to 8 microns with a preferred range of about 20-400 nm. The two major components of Capxol.TM. are unmodified paclitaxel and human serum albumin (HSA). Since HSA is freely soluble in water, Capxol.TM. can be reconstituted to any desired concentration of paclitaxel limited only by the solubility limits for HSA. Thus Capxol.TM. can be reconstituted in a wide range of concentrations ranging from dilute (0.1 mg/ml paclitaxel) to concentrated (20 mg/ml paclitaxel). This can result in fairly small volumes of administration.

Detailed Description Text (10):
It was surprisingly found that the Taxol vehicle, Cremophor/Ethanol diluted in saline, alone caused severe hypersensitivity reactions and death in several dose groups of mice. No such reactions were observed for the Capxol groups at equivalent and higher doses. Thus Capxol, a formulation of paclitaxel that is free of the Taxol vehicle is of substantial advantage.

Detailed Description Text (19):
Capxol.TM. is a lyophilized powder containing paclitaxel and human serum albumin. Due to the nature of the colloidal solution formed from reconstitution of the lyophilized powder toxic emulsifiers such as cremophor (in the BMS formulation of paclitaxel) or polysorbate 80 (as in the Rhone Poulenc formulation of docetaxel) and solvents such as ethanol to solubilize the drug are not required. Removing toxic emulsifiers will reduce the incidences of severe hypersensitivity and anaphylactic reactions that are known to occur in products TAXOL.

Detailed Description Text (132):
To our surprise, it was found that the vehicle, Cremophor/Ethanol alone caused severe hypersensitivity reactions and death in several dose groups of mice. The LD50 data for the TAXOL vehicle alone shows that it is considerably more toxic than Capxol and significantly contributes to the toxicity of TAXOL. It has been unclear in the literature, the cause of hypersensitivity, however, based on these data, we believe that HSR's can be attributed to the Taxol vehicle.

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L9: Entry 46 of 89 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5981564 A

**** See image for Certificate of Correction ****

TITLE: Water-soluble derivatives of paclitaxel, method for producing same and uses thereof

Brief Summary Text (5):

Paclitaxel is a natural product extracted from the bark of the Pacific yew (Taxus brevifolia). It was thereafter found in other members of the Taxacae family including the yew of Canada (Taxus canadensis) found in Gaspesia, eastern Canada and Taxus baccata found in Europe whose needles contain paclitaxel and analogs and hence provide a renewable source of paclitaxel and derivatives. The crude extract was tested for the first time during the 60s and its active principle was isolated in 1971 by Wani et al. who at the same time identified its chemical structure. It showed a wide range of activity over melanoma cells, leukemia, various carcinomas, sarcomas and non-Hodgkin lymphomas as well as a number of solid tumors in animals. Clinical studies show that paclitaxel is a promising anti cancer agent. Paclitaxel is a microtubule blocker, but unlike other drugs inhibiting the mitosis by interaction with microtubules such as colchicin, vincristin and podophyllotoxin, paclitaxel does not prevent tubulin assembly. It rather accelerates the tubulin polymerization and stabilizes the assembled microtubules. The drug acts in a unique way which consists in binding to microtubules, preventing their depolymerization under conditions where usually depolymerization occurred (dilution, calcium, cold and microtubules disrupting drugs). Paclitaxel blocks the cell cycle at prophase which results in an accumulation of cells in G2+M. Because of its unique structure and mechanism of action, paclitaxel was submitted to clinical trials. Interesting activity against many tumors, especially breast cancer and ovarian cancer refractory to chemotherapy, has been observed. However, because of its poor solubility in water, the product had to be administered in ethanol, Cremophor-EL and 5% sucrose diluted in saline or water. Cremophor-EL was responsible for hypersensitivity reactions observed in several patients (Rowinsky, E. K., et al., J. Nat. Can. Inst., 82 (15), 1247-1259). Premedication with anti-histamines had to be administered in order to reduce the toxicity.

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L9: Entry 47 of 89 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977163 A
**** See image for Certificate of Correction ****
TITLE: Water soluble paclitaxel prodrugs

Brief Summary Text (6):
Paclitaxel is typically formulated as a concentrated solution containing paclitaxel 6 mg per milliliter of Cremophor EL (polyoxyethylated castor oil) and dehydrated alcohol (50% v/v) and must be further diluted before administration (Goldspiel, 1994). The amount of Cremophor EL necessary to deliver the required doses of paclitaxel is significantly higher than that administered with any other drug that is formulated in Cremophor. Several toxic effects have been attributed to Cremophor, including vasodilation, dyspnea, and hypotension. This vehicle has also been shown to cause serious hypersensitivity in laboratory animals and humans (Weiss et al., 1990). In fact, the maximum dose of paclitaxel that can be administered to mice by i.v. bolus injection is dictated by the acute lethal toxicity of the Cremophor vehicle (Eiseman et al., 1994). In addition, Cremophor EL, a surfactant, is known to leach phthalate plasticizers such as di(2-ethylhexyl) phthalate (DEHP) from the polyvinylchloride bags and intravenous administration tubing. DEHP is known to cause hepatotoxicity in animals and is carcinogenic in rodents. This preparation of paclitaxel is also shown to form particulate matter over time and thus filtration is necessary during administration (Goldspiel, 1994). Therefore, special provisions are necessary for the preparation and administration of paclitaxel solutions to ensure safe drug delivery to patients, and these provisions inevitably lead to higher costs.

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